IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Alice A. Jacobs et al. Art Unit : 1637
Serial No. : 09/996,056 Examiner : Kenneth R. Horlick
Filed : November 27, 2001
Title : CLINICALLY INTELLIGENT DIAGNOSTIC DEVICES AND METHODS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

I, Andrew B. Onderdonk Ph.D., declare as follows.

1. I am the Director of the Clinical Microbiology Laboratory at Brigham and Women's Hospital and am a Professor of Pathology at Harvard Medical School, both in Boston, Massachusetts. I am also the Editor-in-Chief of the Journal of Microbiology and am a reviewer or editor of several other journals. My curriculum vitae is attached hereto as Exhibit A.

2. I received a Ph.D. in Microbiology in 1973, and have worked in the fields of clinical microbiology and infectious diseases ever since. My major research interests include the role of human microflora in health and disease, in vivo and in vitro models of colonization and infection, and antimicrobial efficacy.

3. The assignee of the Jacobs et al. patent application captioned above ("the Jacobs application") is GeneVention L.L.C., which is now known as Intelligent Medical Devices, Inc. ("IMD"), and is located in Cambridge, MA. I have worked on a consulting basis with IMD since

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about May 2003. In particular, I have worked with IMD on various grant proposals, and have provided them with a number of anonymous patient respiratory samples that contain specific known viruses. Based on my interactions with personnel from IMD, I am familiar with IMD's symptom-specific disease diagnostic methods and kits.

4. I have reviewed the Jacobs application as well as an amended set of claims that applicants propose to file with the United States Patent & Trademark Office ("USPTO") on or after January 7, 2005 ("the proposed claims"). A copy of the proposed claims is attached as Exhibit B.

5. I understand that the USPTO has indicated that certain claims of the Jacobs application are identically described by, or obvious to one of ordinary skill in the relevant field in view of, U.S. Patent No. 6,083,763 to Balch (the "Balch patent"). To better understand this rejection, I have reviewed the Balch patent.

6. Based on my knowledge and experience, my review of the Balch patent, and my understanding of the invention in the Jacobs application as articulated in the proposed claims, I believe that the proposed claims cover an invention that is distinct from any subject matter disclosed in the Balch patent. Furthermore, I believe that the proposed claims would not have been obvious to one of skill in the medical diagnostics field in view of the Balch patent.

7. Although the Balch patent recites in passing the general notion of a diagnostic test for the cause of a defined set of symptoms (at column 5, lines 17-21), it is clear from the overall context and other portions of the text (e.g., column 34, lines 3-13) that Balch contemplates the use of an array of probes for one type of target, e.g., different infectious agents, such as various viral strains, or different genetic mutations, e.g., for cystic fibrosis, that are the cause of a specific disease. Thus, Balch describes at most a disease-specific array. Balch does not describe or suggest the use of symptom-specific array that includes different probes directed to two or

more very different types of targets that are known to cause a given medical symptom (but could be from various diseases) as recited in the proposed claims. For example, with respect to proposed claim 1, Balch does not describe or suggest an array that includes at least (i) a first probe or set of first probes directed to a first target, wherein the first target comprises one or more markers for one or more infectious agents known to cause the one or more medical symptoms; and (ii) a second probe or set of second probes directed to a second target, wherein the second target comprises one or more genetic markers of the subject or one or more biological or chemical molecules, all known to be a cause of the one or more medical symptoms. Balch simply does not describe or suggest anything other than the concept of a disease-specific array for one type of target. The Jacobs application, which covers methods of using symptom-specific arrays is a significant improvement over this simple Balch concept.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date: 1/7/05

Andrew B. Onderdonk, Ph.D.

10/21/2004 9:46:14 AM

CURRICULUM VITAE

Name: Andrew B. Onderdonk

Office Address: Channing Laboratory, 181 Longwood Ave., Boston MA 02115

Address: 28 Lynn Terrace, Westwood MA 02090

Place of Birth: Hartford, Connecticut

Education:

1969	B.A.	MacMurray College
1971	M.S.	Microbiology, University of Missouri
1973	Ph.D.	Microbiology, University of Missouri

Postdoctoral Training:

1973-1975 PHS Postdoctoral Fellow, Infectious Diseases Service, Department of Medicine UCLA, Los Angeles, CA

Licensure and Certification:

1988-1994 Clinical Laboratory Director, City of New York
1988 Clinical Laboratory Director, Bacteriology and Parasitology, State of New York
1991 Clinical Laboratory Director, National Certification Agency for Medical Laboratory Personnel, Washington, DC.

Academic Appointments:

1977-1981 Assistant Professor of Medicine, Tufts University, Boston, MA
1978-1981 Assistant Professor of Microbiology, Tufts University, Boston, MA
1979-1981 Assistant Professor of Veterinary Medicine, Tufts University, Boston,MA
1981-1982 Associate Professor, Dept of Comp Med, Tufts University, Boston, MA
1981-1990 Associate Professor, Microbiology, Tufts University, Boston, MA

1981-1990	Associate Professor of Veterinary Medicine, Tufts University, Boston, MA
1982-1990	Associate Professor, Pathology, Tufts University, Boston, MA
1984-1990	Lecturer, Harvard University, Boston, MA.
1990-2000	Associate Professor of Pathology, Harvard Medical School, Boston,MA
2000-present	Professor of Pathology, Harvard Medical School. Boston, MA

Hospital Appointments:

1975-1979	Scientific and Special Staff, Tufts New England Medical Center, Boston
1990-present	Staff Member, Department of Pathology, Brigham and Women's Hospital, Boston, MA
1990-present	Staff Member, Division of Infectious Diseases, Brigham and Women's Hospital, Boston, MA
1990-present	Director, Clinical Microbiology Laboratory, Brigham and Women's Hospital, Boston, MA

Other Professional Positions and Major Visiting Appointments:

1971-present	Consultant, Labline Industries, Melrose Park, IL
1975-1987	Consultant, Scott Laboratories, Fiskeville, RI
1977	Consultant, Upjohn Pharmaceuticals, Ann Arbor, MI
1979-1980	Acting Director, Veterinary Diagnostic Laboratory, Tufts University School of Veterinary Medicine, Boston, MA
1980-1989	Director, Veterinary Diagnostic Laboratory, Tufts University School of Veterinary Medicine, Boston, MA
1982	Consultant, Veterans Administration Central Office Research
1983-1997	Consultant, Tambrands Inc., Palmer, MA
1983	Consultant, Searle, Ltd., London, UK
1985	Consultant, Canadian Research Council, Toronto, Canada
1986-1988	Consultant, National Ileitis and Colitis Foundation
1987-1990	Director, Division of Laboratories, Tufts University School of Veterinary Medicine, Boston, MA
1988	Institutional Review Team, College of Life Sciences and Agriculture,University of New Hampshire, Durham, NH
1988-present	Member, Scientific Advisory Board, Alpha Beta Technology, Worcester, MA
1991-1993	Consultant, Adams Scientific, Fiskeville, RI
1992-present	Consultant, SmithKline Beecham, Parsippany, NJ
1994-present	Consultant, PML Microbiologics Inc., Tualanin, OR
1991-present	Science by Mail Scientist, Museum of Science, Boston, MA
1998-present	Consultant, Procter and Gamble, Cincinnati, OH
1997-present	Consultant, Genzyme Corporation, Cambridge, MA

1998-present Consultant, Osmetech Ltd, Crewe, England

Major Administrative Responsibilities:

1990-present Director, Clinical Microbiology Laboratory, Brigham and Women's Hospital, Boston, MA
1990-present Director, Anaerobe Research Laboratory, Channing Laboratory, Boston, MA

Major Committee Assignments:

Medical/Veterinary School:

1979-1981 Curriculum Committee, Tufts University School of Veterinary Medicine, Boston, MA
1980-1983 Admissions Committee, Tufts University School of Veterinary Medicine, Boston, MA
1985-1987 Curriculum Committee, Tufts University School of Veterinary Medicine, Boston, MA
1985-1988 Basic Science Tenure and Promotions Committee, Tufts University, Schools of Medicine, Veterinary Medicine, and Dental Medicine, Boston, MA
1985-1989 Chairman, Faculty Council, Tufts University School of Veterinary Medicine, Boston, MA
1994-1995 Member, Harvard University Committee on Microbiologic Safety/Committee for Research on Hazardous Biologic Agents (COMS/CRHBA)
1996-1998 Associate Chair COMS/CRHBA
1998-present Chair, Committee on Microbiologic Safety/Committee for Research on Hazardous Biologic Agents (COMS). This committee is charged with the responsibility for setting policy and determining the safety of research with any biologic agent or microorganism with infectious or hazardous potential for investigators, human subjects or the general public. The committee reviews each submitted protocol, determines an appropriate safety level and approves the research within the guidelines recommended. During my term as Chair of this committee, the complexity of issues facing the committee has increased dramatically. This committee was first established to deal primarily with laboratory based research using biologic agents, including recombinant organisms and vectors, as well as xenografts of tissues and cells in animal test systems. More recently, these recombinant vectors and xenografting strategies have been applied to human disease. Protocols for the use of xenotransplantation and for gene therapy in human subjects have resulted in substantial alterations in operating procedures for the committee and has led to the

establishment of two subcommittees, one for scientific review of gene therapy protocols and a second for scientific review of xenotransplantation protocols. Both subcommittees make recommendations to COMS, with the ultimate decision on safety made by COMS. In addition, I have formalized the policies used by COMS as part of a policy manual and I am in the process of seeking to clarify the role of this committee within the university research framework.

Hospital:

1991-present	Education Committee, Clinical Laboratories, Brigham and Women's Hospital
1994-present	Laboratory Utilization Committee, Brigham and Women's Hospital
1994-1997	Cost Management Learning Center, Brigham and Women's Hospital
1997-1998	Laboratory Consolidation Committee, Brigham and Women's Hospital
1998-present	Clinical Pathology resident Research Committee

Professional Society Involvement:

1973-present	Member, Society of Microbial Ecology and Disease
1988-present	Member, International Society for Anaerobic Bacteria
1973-present	Member, American Society for Microbiology
1975-present	Member, Northeast Branch, American Society for Microbiology
1976-present	Member, American Federation for Clinical Research
1977-present	Member, American Association for the Advancement of Science
1980-1989	Member, American Association of Veterinary Laboratory Diagnosticians
1981-present	Fellow, American Academy of Microbiology
1983	Co-Chairman, 8th International Symposium on Intestinal Microecology, Boston, MA
1986	Organizing Committee, International Symposium on Anaerobic Bacteria and Bacterial Infections. Monte Carlo, Monaco
1977-present	Fellow, Infectious Diseases Society of America
1990-present	Member, New York Academy of Science
1992-present	Member, The Academy of Clinical Laboratory Physicians and Scientists
1993	Chairman, Organizing Committee Society for Microbial Ecology and Disease, Boston, MA
1994-1995	Chairman, Organizing Committee for First World Congress on Anaerobic Bacteria and Bacterial Infections, San Juan, Puerto Rico
1996-1998	Chairman, Organizing Committee for 2nd World Congress on Anaerobic Bacteria and Bacterial Infections, Nice, France
1999-present	Chairman, Organizing Committee for World Congress on Anaerobic Bacteria and Bacterial Infections

Editorial Boards:

1984-93	Editorial Board, Infection and Immunity
1985-present	ad hoc Reviewer, New England Journal of Medicine
1989-93	Editorial Board, Journal of Clinical Microbiology
1989-present	ad hoc Reviewer, Journal of Infectious Diseases
1990-present	ad hoc Reviewer, Applied and Environmental Microbiology
1990-present	ad hoc Reviewer, Gastroenterology
1990	Guest Editor, Reviews of Infectious Diseases Supplement,
1993-99	Editor, Journal of Clinical Microbiology
1994-present	Editorial Board, Anaerobe
1998-99	Editorial Board, Clinical Microbiology Reviews
1999-present	Editor-in-Chief, Journal of Clinical Microbiology

Awards and Honors:

1973	Who's Who Among Students in American Universities and Colleges
1973	Co-Chairman, Advisory Board to the President of the University of Missouri
1973	Member, Selection Committee Dean of Student Affairs, University of Missouri
1976	Member, Sigma Xi
1976	Alumni Board of MacMurray College
1978	Vice President, Northeast Branch, American Society for Microbiology
1982-1984	President, Northeast Branch, American Society for Microbiology
1990-1996	Treasurer, International Society for Anaerobic Bacteria
1990-1992	President, Society for Microbial Ecology and Disease
1997-present	President, International Society for Anaerobic Bacteria
1999	Distinguished Alumni Award, MacMurray College

Report of Research:

Major research interests:

1. Role of human microflora in health and disease
2. Pathogenesis of obligate anaerobes
3. In vivo and in vitro models of colonization and infection
4. Antimicrobial efficacy
5. Immunomodulators as anti-infective agents

Narrative description of research:

My research encompasses several areas related to human microbial flora and its role in health and disease. My interests include the pathogenesis of obligately anaerobic microorganisms, the in vivo and in vitro modeling of both normal microflora and pathogenic microorganisms, and the evaluation and development of new therapeutic agents, including antibiotics and immunomodulators.

Over twenty years ago, an animal model simulating human intraabdominal sepsis was developed in our laboratory. This model has been used to document the role of both obligate anaerobes and facultative species during the infectious process, as well as serving as a highly predictive model for antimicrobial efficacy evaluation during a mixed infection containing both obligate anaerobes and facultative bacterial species. This model system has also been used extensively to study the pathogenesis of *Bacteroides fragilis*. The primary role of this organism in abscess development was defined and its principal virulence factor, the capsular polysaccharide, was identified in collaborative studies with Dr. Dennis Kasper. Subsequent studies spanning two decades have focused on the immunologic basis for abscess development and prevention in this model system and, more recently, evaluation of the genetics of capsule production.

My interest in inflammatory bowel diseases has resulted in ongoing studies using both animal and human models for IBD. Based on my studies of the carrageenan model for ulcerative colitis, a specific microbial component of the intestinal microflora, *Bacteroides vulgatus*, was identified as being capable of provoking ulcerations in gnotobiotic animals. These early studies allowed me to develop the quantitative microbiologic techniques that have been widely used for other human microflora studies. Our studies of antibiotic associated colitis in a hamster model led to the isolation and identification of the causative agent of this toxin mediated disease, *Clostridium difficile*. Subsequent work, in collaboration with Dr. John Bartlett, resulted in the identification of the same agent as causing human disease. Studies of ileal pouch disease in humans following surgical construction of pouch reservoirs has identified bacterial overgrowth as a potentially significant factor in the development of ileal pouchitis. My recent studies have included evaluation of the intestinal microflora of the HLA-B27 transgenic rat during development of a characteristic inflammatory bowel disease. It is of interest to note that other investigators have shown the importance of *B. vulgatus* to the development of experimental IBD in other transgenic animals. My interest and research in this area is ongoing.

Based on quantitative and qualitative vaginal microflora studies conducted as part of the assessment of the role of catamenial products in toxic shock syndrome, we have developed both predictive statistical models for vaginal microflora and in vitro continuous culture models that simulate normal and abnormal conditions. These modeling techniques have been shown to be highly predictive of both normal and abnormal vaginal microflora and are currently being used to simulate the vaginal microflora in an effort to understand the role of the

various microbial species as they relate to preterm delivery, the development of bacterial vaginosis and maintenance of a healthy vaginal micro environment.

The animal models developed in this laboratory have been used to assess the therapeutic efficacy of a variety of anti-infective agents. Most recently, we have employed the model for intraabdominal sepsis to examine the role of -glucans as possible immunomodulators. A number of ongoing studies are exploring the nature of immunomodulation and protection against intraabdominal sepsis by a variety of compounds.

Research funding information:

Years	Funding source	Role	Grant Title
1975-1985	NIH	PI	Carrageenan model for experimental ulcerative colitis
1975-1989	UpJohn, Inc.	PI	Drug efficacy studies
1982-1990	NIH/NIAID	Sub-contract	*Bacteroides fragilis*: Pathogenic mechanisms and immunity
1983-1997	Tambrands, Inc.	PI	Vaginal microflora study
1986-1988	Ileitis and Colitis Foundation of America	PI	Experimental ulcerative colitis
1987-1990	Ileitis and Colitis Foundation of America	co-PI	Microflora of biopsies of inflammatory bowel disease
1988-1996	Alpha Beta Technology	PI	In vivo evaluation of the immunomodulatory properties of yeast glucans.
1988-	Roerig/Pfizer	PI	Drug efficacy studies
1989	Smith-Kline French	PI	Drug efficacy tudies
1991-1994	Ileitis and Colitis Foundation of Canada	co-PI	Ileal pouchitis biopsy study
1992-1994	NIH	co-PI	*Bacteroides* capsule mutagenesis: effect on virulence
1993-present	Smith-Kline Beecham	PI	Development of an in vivo model for human vaginal microflora during health and disease.
1995-2000	NIH	co-PI	*Bacteroides fragilis* capsules: synthesis and virulence

1995-present	Pfizer, Inc.	PI	Use of continuous culture for kill kinetics and simulation of mixed microflora
1996-present	Genzyme Corporation	PI	Biologic effects of Seprafilm and Sepragel in an animal model of intraabdominal sepsis
1998-present	Proctor and Gamble	PI	In vivo and in vitro vaginal microflora studies
1998-present	Osmetech plc	PI	Evaluation of microbial volatile fatty acid products
1999-present	NIH	PI	QuantitativeMicrobiologic Model for Preterm Delivery
2003-present	NIH	co-PI	New England Regional Center for Excellence (NERCE) for Biodefence and Emerging Infectious Disease Research

Report of Teaching:

Local Contributions:

Medical School Courses:

1990	HMS IMD Course, Instructor 20 students 8 hours preparation,14 hour course
1991	HMS Human Systems Lecturer 160 students 4 hours preparation, 45 min lecture
1992	HMS IMD Course, Instructor 20 students 8 hours preparation,14 hour course
1993	HMS Human Systems Lecturer 160 students 4 hours preparation,45 min lecture

1993	HMS IMD Course Instructor 20 students 8hours preparation,14 hour course
1994	HMS Human Systems Lecturer 160 students 4 hours preparation, 45 min lecture
1995	HMS IMD Course Instructor 20 students 8 hours preparation, 14 hour course
1995	HMS Human Systems Lecturer 160 students 4 hours preparation, 45 min lecture
1996	HMS IMD Course Instructor 20 students 8 hours preparation,14 hour course
1998-1999	HMS IMID Tutorial Tutor

Invited Teaching Presentations

1996	Anaerobic Infections Presentation, Surgical Grand Rounds 100-150 medical staff 4 hours preparation, 1 hour presentation

Advisory and Supervisory responsibilities in Clinical or Laboratory Setting

1990- present	Teaching, training and evaluation of pathology residents in Clinical Microbiology, Brigham and Women's Hospital 3-5 Residents 120 hours/year
1981- present	Responsible for the teaching, training and evaluation of 1-2 postdoctoral fellows /year in the Anaerobe Research Laboratory, 300 hours/year.

Postdoctoral Fellows Trained:

1981-1982	Michael Shapiro, M.D. , in collaboration with Dennis Kasper, M.D., current position, Department of Surgery, BIDMC, Boston, MA
1984-1985	Dori Zalesnik, M.D., in collaboration with Dennis Kasper,M.D., current position, Division of Infectious Diseases, Beth Israel Hospital, Boston, MA
1987-1988	Arnold Zedd, M.D., current position, private practice.
1988-1989	James Breeling, M.D., in collaboration with Dennis Kasper, M.D., current position, Associate Chief of Medicine, VA Medical Center, West Roxbury, MA
1988-1990	Joanne Lindenmayer, D.V.M., Medical Foundation Scholar, current position, Instructor, Tufts University School of Veterinary Medicine.
1989-1990	Annalisa Pantosti, M.D., Istituto di Superiore, Rome, 12 month training program supported by the Italian Ministry of Health, current position, Research investigator, Istituto di Superiore, Rome Italy
1991-1993	Robin Ross, Ph.D., current position, Research Associate, Department of Medicine, Brigham

	and Women's Hospital and Channing Laboratory, HMS, Boston, MA
1990-1992	Arthur O. Tzianabos, Ph.D., in collaboration with Dennis Kasper, M.D., current position; Assistant Professor, Department of Medicine , Brigham and Women's Hospital and Channing Laboratory, HMS, Boston, MA
1994-1997	Frank Gibson, Ph.D., current position; Instructor, Boston University, Boston, MA
1994-1998	Vivien Pybus, Ph.D., Current position; Instructor, Children's Hospital, Boston, MA
1998-2000	Gabrielle Schwartzenberger, M.D., Current position; staff physician, Austria
2000-2002	Tetsuya Matsumoto, M.D., Current position; assistant professor of medicine, University of Tokyo School of Medicine
2000-2004	Begonia Ruiz, PhD. Current position, Instructor Harvard Medical School
2003-2004	Hiroshige Mikamo, Current position; Associate Professor of Medicine, Gifu Medical School

Regional National or International Contributions (last 4 years only):

Invited Presentations:

1995	Models for Vaginal Microflora, San Juan, Puerto Rico. World Congress on Anaerobic Infections
1995	Animal Models for IBD. Den Haag, Holland. Falk Foundation
1995	Polysaccharide Capsule of *B. fragilis*. Madrid, Spain. Surgical Infections Conference
1996	Microbiologic Studies of Ileal Pouch Disease. Ottawa, Canada. Trends in Inflammatory Bowel Disease

1997 Experimental Models for Assessing Antibiotic Efficacy. Munich, Germany. International Congress on Immune Consequences of Trauma, Shock and Sepsis

1998 Role of Intestinal Microflora in IBD, Falk Foundation Symposium, Tbilisi, Georgia

1998 New Therapeutic Agents for Surgical Infections SEAMA Symposium, Phuket, Thailand

Professional Leadership Roles

1973 Founder and Past President: Society for Microbial Ecology and Disease

1988 Co-founder: International Society for Anaerobic Bacteria

BIBLIOGRAPHY

Original Articles:

1. Maier BR, Onderdonk AB, Baskett RC, Hentges DJ. *Shigella* indigenous flora interactions in mice. Amer J Clin Nutr 1972;25:1433-1440.

2. Rubenstein E, Onderdonk AB, Rahal JJ. Peritonsillar infection and bacteremia caused by *Fusobacterium gonodiaformans*. J Pediat 1974;85:673-675.

3. Weinstein WM, Onderdonk AB, Bartlett JG, Gorbach SL. Experimental intraabdominal abscesses in rats. Development of animal model. Infect Immun 1974;10:1250-1255.

4. Onderdonk AB, Weinstein WM, Sullivan NM, Bartlett JG, Gorbach SL. Experimental intraabdominal abscesses in rats: Quantitative bacteriology of infected animals. Infect Immun 1974;10:1256-1259.

5. Bartlett JG, Bustetter LA, Gorbach SL, Onderdonk AB. Comparative effect of tetracycline and doxycycline on the occurrence of resistant *Escherichia coli* in the fecal flora. Antimicrob Agents Chemother 1975;7:55-57.

6. Mayhew JW, Onderdonk AB, Gorbach SL. Effects of time and growth on short chain fatty acid production by *Bacteroides fragilis*. Appl Microbiol 1975;29:472-475.

7. Weinstein WM, Onderdonk AB, Bartlett JG, Louie TJ, Gorbach SL. Antimicrobial therapy of experimental intraabdominal sepsis. J Infect Dis 1975;132:282-286.

8. Gorbach SL, Mayhew JW, Bartlett JG, Thadepalli H, Onderdonk AB. Rapid diagnosis of anaerobic infections by direct gas liquid chromatography of clinical specimens. J Clin Invest 1976;57:478-484.

9. Onderdonk AB, Bartlett JG, Louie TJ, Sullivan-Sigler N, Gorbach SL. Microbial synergy in experimental intraabdominal abscess. Infect Immun 1976;13:22-26.

10. Onderdonk AB, Johnston J, Mayhew JW, Gorbach SL. Effect of dissolved oxygen and Eh on *Bacteroides fragilis* during continuous culture. Appl Environ Microbiol 1976;31:168-172.

11. Onderdonk AB, Hermos JA, Bartlett JG. The role of the intestinal microflora in experimental colitis. Am J Clin Nutr 1977;30:1819-1925.

12. Louie TJ, Onderdonk AB, Gorbach SL, Bartlett JG. Therapy for experimental intraabdominal sepsis: Comparison of four cephalosporins with clindamycin plus gentamicin. J Infect Dis 1977;135:S18-S22.

13. Bartlett JG, Onderdonk AB, Drude E, Goldstein C, Anderka M, Alpert S, McCormack WH. Quantitative microbiology of the vaginal flora. J Infect Dis 1977;132:271-277.

14. Onderdonk AB, Kasper DL, Cisneros RL, Bartlett JG. The capsular polysaccharide of *Bacteroides fragilis* as a virulence factor: Comparison of the pathogenic potential of encapsulated and unencapsulated strains. J Infect Dis 1977;136:82-89.

15. Bartlett JG, Onderdonk AB, Cisneros RL: Clindamycin-associated colitis in hamsters: Protection by vancomycin. Gastroenterology 1977;73:772-776.

16. Onderdonk AB, Polk BF, Moon NE, Goren B, Bartlett JG. Methods for quantitative vaginal flora studies. Am J Obstet Gynecol 1977;128:777-781.

17. Kasper DL, Onderdonk AB, Bartlett JG. Quantitative determination of the antibody response to capsular polysaccharide of *Bacteroides fragilis* in an animal model of intraabdominal abscess formation. J Infect Dis 1977;136:789-795.

18. Sheckman P, Onderdonk AB, Bartlett JG. Anaerobes in spontaneous peritonitis. Lancet 1977;2:1223.

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20. Kasper DL, Hayes ME, Reinap BG, Craft FO, Onderdonk AB, Polk BF. Isolation and identification of encapsulated strains of *Bacteroides fragilis.* J Infect Dis 1977;136:75-81.

21. Onderdonk AB, Moon NE, Kasper DL, Bartlett JG. Adherence of *Bacteroides fragilis* in vivo. Infect Immun 1978;19:1083-1087.

22. Bartlett JG, Chang TW, Gurwith M, Gorbach SL, Onderdonk AB. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. N Engl J Med 1978;298:531-534.

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Bartlett JG. Anaerobic microflora of the vaginal flora of children. Amer J Obstet Gynecol 1978;131:853-856.

25 Mansheim BJ, Onderdonk AB, Kasper DL. Immunochemical and biologic studies of the lipopolysaccharide of *Bacteroides melaninogenicus* subspecies *assacharolyticus*. J Immunol 1978;120:72-78.

26. Bartlett JG, Moon NE, Goldstein PR, Goren B, Onderdonk AB, Polk BF. Cervical and vaginal bacterial flora: Ecological niches in the female lower genital tract. Am J Obstet Gynecol 1978;130:658-662.

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42. Kasper DL, Onderdonk AB, Reinap GB, Lindberg AA. Variations of *Bacteroides fragilis* with in vivo passage: presence of an outer membrane associated glycan and loss of capsular antigen. J Infect Dis 1980;142:750-756.

43. Onderdonk AB, Franklin ML, Cisneros RL. Production of experimental ulcerative colitis in gnotobiotic guinea pigs with simplified microflora. Infect Immun 1981;32:277-231.

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Applicant : Alice A. Jacobs et al. Art Unit : 1637
Serial No. : 09/996,056 Examiner : Jeffrey Siew
Filed : November 27, 2001
Title : CLINICALLY INTELLIGENT DIAGNOSTIC DEVICES AND METHODS

PROPOSED CLAIMS AS OF JANUARY 7, 2005

1. (Currently amended): A method of determining a cause of one or more medical symptoms exhibited by a subject, the method comprising:

(a) obtaining one or more ~~a~~ biological samples from the subject;

(b) obtaining an array of different probes or different sets of probes, wherein each probe or set of probes selectively interacts with a target associated with a different known cause of the one or more medical symptoms, and wherein the array includes at least

(i) a first probe or set of first probes directed to a first target, wherein the first target comprises one or more markers for one or more infectious agents known to cause the one or more medical symptoms; and

(ii) a second probe or set of second probes directed to a second target, wherein the second target comprises one or more genetic markers of the subject or one or more biological or chemical molecules, all known to be a cause of the one or more medical symptoms;

(c) applying the one or more biological samples to the probes in the array under conditions that enable all of the probes to selectively interact with any targets in the biological sample;

(d) detecting interactions; and

(e) analyzing interactions to determine a cause of the one or more medical symptoms.

2. (Original): The method of claim 1, wherein the array of probes or sets of probes is arranged on a planar substrate.

3. (Original): The method of claim 1, wherein each target is a nucleic acid, peptide, polypeptide, protein, antibody, antigen, small organic molecule, inorganic molecule, enzyme, or polysaccharide.

4. (Original): The method of claim 1, wherein the array of probes comprises nucleic acid probes and polypeptide probes.

5. (Original): The method of claim 1, wherein all of the probes in the array are polypeptides.

6. (Original): The method of claim 5, wherein the probes are antibodies, antigens, enzymes, zinc-finger binding proteins, minor-groove binders, transcriptional factors, combinations thereof, or chimeras thereof.

7. (Original): The method of claim 1, wherein the subject is a plant or animal.

8. (Original): The method of claim 1, wherein the subject is a human.

9. (Original): The method of claim 1, wherein the subject is deceased.

10. (Currently amended): The method of claim 1, wherein the array includes four or more different probes or sets of probes, wherein each probe or set of probes is directed to a different target, and wherein the different first and second targets comprise at least a marker for a virus, a marker for a bacteria, a biological molecule, and a genetic marker of the subject.

11. (Original): The method of claim 1, wherein the biological sample is a blood, cerebrospinal fluid, cell culture, urine, sweat, buccal swab, tissue biopsy, or aspiration sample.

12. (Original): The method of claim 2, wherein the probes are attached to the substrate using covalent or non-covalent bonds.

13. (Original): The method of claim 2, wherein the probes are attached to the substrate using amide or thiol bonds.

14. (Original): The method of claim 1, wherein the probes are expressed on the surface of genetically modified cells.

15. (Original): The method of claim 1, wherein a probe selectively interacts with a target by specifically binding to the target to form a complex.

16. (Original): The method of claim 1, wherein a first probe selectively interacts with a target associated with an infectious disease caused by a bacteria, virus, or fungus, and a second, different probe selectively interacts with a target associated with a genetic cause.

17. (Currently amended): The method of claim 1, wherein the array of probes further comprises probes that assay for the absence of a causative agent of one or more medical symptoms.

18 and 19. (Canceled)

20. (Original): A method of claim 1, wherein all of the probes selectively interact with their respective targets under the same conditions.

21. (Canceled):

22. (Currently amended): The method of claim 49, wherein the therapeutic optimization factor is tolerance, intolerance, or susceptibility of the subject or an infectious agent to a specific drug.

23. (Currently amended): The method of claim 49, wherein the marker for the therapeutic optimization factor is a gene in a pathogen that causes susceptibility, resistance, or an idiosyncratic reaction of the pathogen when exposed to a therapeutic agent.

24 to 34. (Cancelled)

35 to 39. (Withdrawn)

40. (Canceled)

41. (Previously Presented): The method of claim 1, wherein the array of probes comprises nucleic acid probes.

42. (New): The method of claim 1, wherein all of the probes in the array are nucleic acid probes.

43. (New) The method of claim 1, wherein the array further comprises a third probe or set of third probes directed to a third target, wherein the third target comprises a marker for a therapeutic optimization factor of the subject, a marker for a therapeutic optimization factor of the first target, or both.

44. (New) The method of claim 1, wherein the biological or chemical molecule is a cancer marker, vascular marker, inflammatory marker, endocrine marker, metabolic marker, or autoimmune marker.

45. (New) The method of claim 1, wherein the biological or chemical molecule is an immunoglobulin, self-antigen, or antigen.

46. (New) The method of claim 1, wherein the biological or chemical molecule is a poison, drug, or a small organic or inorganic molecule.

47. (New) The method of claim 1, wherein the infectious agent is a virus, bacteria, fungus, or pathogenic plant.

48. (New) The method of claim 1, further comprising determining the susceptibility of the subject to a cause of the one or more medical symptoms; wherein the array further includes a third probe or set of third probes directed to a third target, wherein the third target comprises one

or more genetic markers or proteins associated with the susceptibility of the subject to a cause of the one or more medical symptoms; and wherein analyzing further comprises analyzing interactions to determine the susceptibility of the subject to a cause of the one or more medical symptoms.

49. (New) The method of claim 1, further comprising assessing the suitability of one or more therapeutic agents to treat the cause of the one or more medical symptoms; wherein the array further includes a third probe or set of third probes directed to a third target, wherein the third target comprises one or more markers for one or more therapeutic optimization factors; and wherein analyzing further comprises analyzing interactions to determine the suitability of a therapeutic agent to treat a cause of the one or more symptoms.

50. (New) The method of claim 49, wherein the third target comprises one or more markers for one or more therapeutic optimization factors for (i) two or more of the first target, (ii) two or more of the second target, or (iii) one or more of each of the first and second targets.

51. (New) The method of claim 48, further comprising assessing the suitability of one or more therapeutic agents to treat the cause of the one or more medical symptoms; wherein the array further includes a fourth probe or set of fourth probes directed to a fourth target, wherein the fourth target comprises one or more markers for one or more therapeutic optimization factors; and wherein analyzing further comprises analyzing interactions to determine the suitability of a therapeutic agent to treat a cause of the one or more symptoms.